



Nebivolol (Bystolic), a Novel Beta Blocker for Hypertension

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INTRODUCTION

Hypertension is an asymptomatic condition of persistently elevated blood pressure (BP) that affects approximately 50 million Americans and one billion people worldwide.^{1,2} It has been associated with other diseases and events such as myocardial infarction (MI), heart failure, stroke, and kidney disease.¹ Although hypertension the most common primary care diagnosis in the U.S., most patients are undertreated (fewer than 60% of patients receive any treatment),^{1,3-6} and only about 31% have BP that is adequately controlled.³

The management of hypertension involves lifestyle modifications, pharmacological treatment, or both. Weight reduction for overweight or obese patients, adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, moderate consumption of alcohol, and physical activity are all essential to decreasing BP and enhancing the efficacy of pharmacotherapeutic regimens.¹

Pharmacological treatment includes management with one or more agents belonging to the following drug classes: thiazide diuretics, beta blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE)-inhibitors, and angiotensin receptor blockers (ARBs).

These medications can reduce BP as well as the complications of hypertension.^{1,2,7}

Although thiazide diuretics are recommended as the first-line therapy for most patients with hypertension, beta blockers have a compelling indication for use in patients with high-risk conditions such as heart failure, MI, coronary disease, and diabetes.^{1,8} Beta blockers exert antihypertensive effects by reducing myocardial contractility, heart rate, and cardiac output.^{9,10} Central inhibition of sympathetic nervous system outflow, inhibition of the renin-angiotensin system by reducing renin release from the juxtaglomerular apparatus, and resetting or altered sensitivity of baroreceptors may also contribute to the BP-lowering effects of this drug class.⁹⁻¹¹

Beta blockers differ in many of their pharmacological properties, including beta₁- and beta₂-adrenergic receptor selectivity and vasodilatory capabilities. Currently, all available beta blockers can be categorized into one of four principal groups based on their receptor affinity and hemodynamic properties:

- noncardioselective, nonvasodilatory
- cardioselective, nonvasodilatory
- noncardioselective, vasodilatory
- cardioselective, vasodilatory

A fifth category includes nonselective beta blockade with intrinsic sympathomimetic activity; however, this group of agents is not favored for use because of data demonstrating their potential to increase peripheral vascular resistance and to attenuate decreases in heart rate and cardiac output that may negate any benefits in cardiovascular disease.¹⁰

Nebivolol (Bystolic, Forest Laboratories), a third-generation beta blocker, is

approved by the FDA for the treatment of hypertension.¹² The medication's unique chemical structure is composed of a racemic mixture of d-nebivolol and l-nebivolol (Figure 1).¹³ Nebivolol exerts nitric oxide (NO)-mediated vasodilation in addition to conventional beta-blocking effects.

PHARMACOLOGY AND MECHANISM OF ACTION¹³⁻¹⁷

Beta blockers are typically categorized as selective or nonselective to beta receptors. Nebivolol may be considered both, depending on the drug's concentration in the body. At low concentrations, typically achieved in extensive metabolizers (the majority of the population), and at doses of 10 mg and below, nebivolol is beta₁-selective. However, at higher concentrations, in poor metabolizers and at higher doses, nebivolol loses its selectivity and blocks both beta₁ and beta₂ receptors.

Nebivolol also possesses novel vasoactive factors. It provides vasodilation by releasing endothelial nitric oxide. The vasodilation properties result in an overall positive hemodynamic side-effect profile, including cold extremities and a reduction in exercise intolerance.

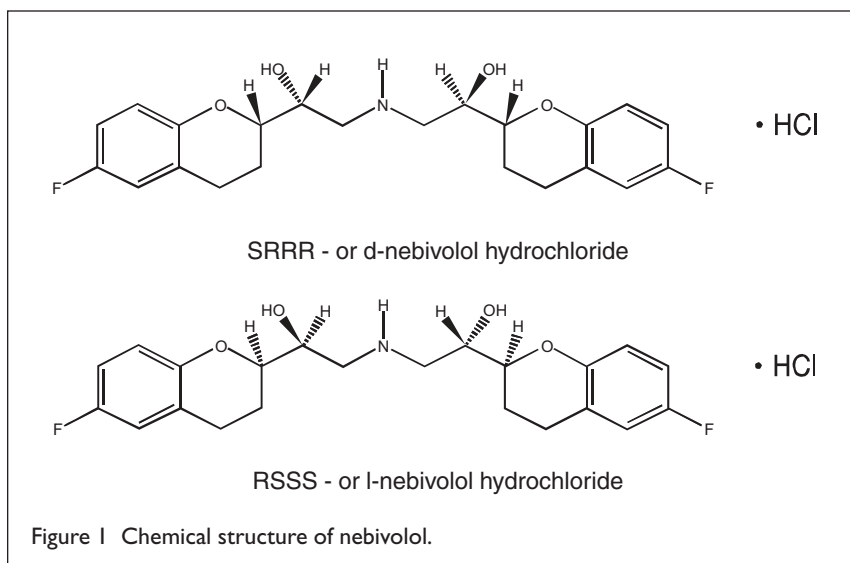
PHARMACOKINETICS AND PHARMACODYNAMICS^{13-16,18}

The pharmacokinetic features of nebivolol vary according to the phenotype of the metabolizer. After a 15-mg dose, peak plasma concentrations were reached at 0.5 to 2 hours in extensive metabolizers and in 3 to 6 hours in poor metabolizers. Absorption of nebivolol is very similar to that of an oral solution. The presence or absence of food does not alter the drug's kinetic profile; therefore, nebivolol may be taken without regard to meals.

Nebivolol is highly protein-bound, mostly to albumin at 98%, independent of its concentrations. The half-life of nebiv-

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olol varies as well: 10.3 hours in extensive metabolizers and 31.9 hours in poor metabolizers.

Nebivolol undergoes extensive first-pass metabolism through the cytochrome P450 2D6 enzyme system. There is a great difference in bioavailability (12% for extensive metabolizers and 96% for poor metabolizers). However, the lower concentration of unchanged drug in extensive metabolizers is balanced by the formation of active hydroxyl metabolites, yielding insignificant clinical differences in therapeutic endpoints.

Metabolism pathways differ according to the phenotype. The predominant metabolic pathway in extensive metabolizers is aromatic hydroxylation, whereby glucuronidation and alicyclic hydroxylation are secondary; *N*-dealkylation is less important. The predominant metabolic pathway in poor metabolizers is glucuronidation and alicyclic hydroxylation; both *N*-dealkylation and aromatic hydroxylation are less important. Nebivolol is excreted mostly as metabolites (38% urine and 44% feces in extensive metabolizers vs. 67% urine and 13% feces in poor metabolizers).

CLINICAL EFFICACY

The FDA's approval of nebivolol was based on its antihypertensive effectiveness in the two pivotal randomized, double-blind, multicenter, placebo-controlled trials conducted in the U.S. Both studies concluded that nebivolol was safe, well tolerated, and effective for patients with mild-to-moderate hypertension.

Weiss et al.¹⁹

A total of 909 patients with a diastolic BP of between 95 and 109 mm Hg received nebivolol 1.25 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg, or placebo once daily for up to 84 days in 70 sites in the U.S. All participants entered a four-week, single-blind, placebo run-in/washout phase following screening and before randomization. The patients were instructed to return to their treatment sites on days 14, 28, 56, and 84. BP and heart rate were monitored, and compliance and the use of concomitant medications were assessed. Concomitant agents that exerted antihypertensive effects were prohibited at all times during the study.

Eighty-five percent (777 patients) completed the study. After 84 days of treatment, all nebivolol groups had significantly higher percentages of patients who responded to therapy (i.e., a diastolic BP of 90 mm Hg or below or a reduction of 10 mm Hg or more from baseline) compared with the placebo group. Significant decreases in peak diastolic and systolic BP were also observed in a dose-dependent manner (least-squares [LS] mean reductions from baseline of 9.1 to 13.9 mm Hg and 7.6 to 14 mm Hg compared with placebo, respectively).

The nebivolol groups, with doses ranging from 1.25 to 20 mg once daily, also had significantly greater LS mean reductions in trough diastolic and systolic BP, compared with placebo patients, from baseline to day 84. Placebo-subtracted LS mean reductions in trough diastolic and systolic BP ranged from 5.1 to 8.3

mm Hg and 6.6 to 11.7 mm Hg, respectively. Little difference was noted in diastolic BP with 2.5 to 20 mg, compared with placebo. No significant differences were observed in the incidence of adverse drug events between treated and placebo groups.

Saunders et al.²⁰

The Saunders study aimed to assess the antihypertensive efficacy of nebivolol at doses of 2.5 mg, 5 mg, 10 mg, 20 mg, or 40 mg once daily in 300 African-American patients with a diastolic BP of between 95 and 109 mm Hg for 12 weeks in 38 sites in the U.S. As a result of evidence suggesting a poor response to monotherapy with beta-blockers in African-Americans, the investigators selected this population in order to investigate their response to a selective vasodilatory beta blocker.

All study participants entered a four-week, single-blind, placebo run-in period with an additional two-week washout period for those previously receiving antihypertensive therapy before randomization into treatment or placebo groups. Patients were assessed on days 14, 28, 56, and 84 at their respective study sites for BP; heart rate, compliance, and the concomitant use of other medications were also evaluated.

Eighty-six percent (259 patients) completed the 12-week treatment period. At the conclusion of the study, patients who received nebivolol doses of 5 mg or more showed significantly higher response rates than the placebo group. Significant decreases in peak diastolic BP (for all doses) and systolic BP (for doses of 5 mg or greater) were also observed. LS mean reductions from baseline were 8.6 to 11.4 mm Hg for diastolic BP and 10.6 to 12.2 mm Hg for systolic BP, compared with placebo. In addition, the nebivolol patients who received doses of 5 mg or more had significantly greater LS mean reductions in trough diastolic BP (7.7–8.3 mm Hg) compared with placebo patients.

Groups receiving 10 mg or more also had significantly lower LS mean reductions in trough systolic BP (6.4–7.2 mm Hg). Placebo-subtracted LS mean reductions in trough diastolic BP from baseline were statistically significant for nebivolol doses of 5 to 40 mg (4.9–5.5 mm Hg), as well as in trough systolic BP for doses of 10 to 40 mg (6–6.8 mm Hg), compared

with patients receiving placebo.

All nebivolol groups showed reductions in trough heart rate, with doses of 10 mg or more being statistically significant compared with placebo. No significant differences were observed in the incidence of ADEs between treated and placebo groups.

Gradman²¹

To assess the efficacy and safety of nebivolol when added to ongoing antihypertensive therapy in patients with mild-to-moderate hypertension, Gradman conducted a 12-week multicenter study of patients receiving a stable regimen of antihypertensive agents, most commonly consisting of an ACE-inhibitor, an ARB, and/or a diuretic. Mild-to-moderate hypertension was defined as a diastolic BP of between 90 and 109 mm Hg. All participants underwent a 14-day screening and a beta-blocker washout period. The 669 patients were then randomly assigned to receive once-daily nebivolol 5 mg, 10 mg, 20 mg, or placebo. BP, tolerability, and compliance were assessed on days 14, 42, and 84.

Eighty-nine percent (598 patients) completed the study. Significantly more patients responded to nebivolol therapy than to placebo. The addition of nebivolol (at any dose) to ongoing antihypertensive therapy produced significant additional reductions in trough diastolic and systolic BP (LS mean reductions from baseline of 6.6 to 7.9 mm Hg and 5.7 to 6.3 mm Hg, respectively) compared with placebo. There were also significant reductions in peak diastolic BP (up to 13.6 mm Hg) and systolic BP (13.3 mm Hg) from baseline with all doses of nebivolol. No significant differences were seen in the incidence of ADEs between treatment and placebo groups.

ADVERSE DRUG REACTIONS^{13,19-21}

Nebivolol was determined to be safe and well tolerated in all studies. The most frequently reported ADEs reported in the previously mentioned studies included headache, dizziness, fatigue, and nasopharyngitis. Other common treatment-emergent events were nausea, diarrhea, constipation, arthralgia, peripheral edema, insomnia, chest pain, bradycardia, dyspnea, dyspepsia, cough, and rash.

DRUG INTERACTIONS^{13,15,16}

Nebivolol should generally be avoided by patients taking other myocardial depressants or atrioventricular conduction inhibitors, specifically dihydropyridine calcium-channel blockers or antiarrhythmic medications, because of the increased risk of bradycardia. In the case of concomitant nebivolol and clonidine (Catapres, Boehringer Ingelheim), nebivolol should be discontinued several days before the clonidine dose is tapered.

CYP 2D6 inhibitors increase plasma levels of nebivolol, whereas CYP 2D6 inducers decrease levels; therefore, caution should be used with combination therapy. Coadministration with the CYP 2D6 inhibitor fluoxetine (Prozac, Eli Lilly), for example, can result in an eight-fold increase in the area-under-the-curve (AUC) concentration and a three-fold increase in the peak concentration (C_{max}) of D-nebivolol. Close monitoring of BP is necessary, and the dose of nebivolol should be adjusted according to therapeutic response. Table 1 presents some substrates, inhibitors, and inducers of nebivolol.²²

Studies have shown that the ACE-inhibitor ramipril (Altace, King) and the loop diuretic furosemide (Lasix, Sanofi-Aventis) have not caused pharmacokinetic changes in drug concentrations. This is important because ACE-inhibitors and loop diuretics are commonly prescribed in combination regimens along with beta blockers. Digoxin and warfarin (Coumadin, Bristol-Myers Squibb) have also been studied in small clinical trials and have not been shown to alter the pharmacokinetic properties of any drugs involved.

CONTRAINDICATIONS¹³

As with most beta blockers, nebivolol is contraindicated in patients with severe bradycardia and greater than first-degree heart block. Nebivolol should also be avoided in patients with cardiogenic shock, acute decompensated heart failure, sick sinus syndrome with no permanent pacemaker, and severe hepatic impairment (Child-Pugh class B).

Nebivolol should not be administered to any patients with a hypersensitivity to any component of the medication.

PRECAUTIONS AND WARNINGS¹³

Because of the variations in the metabolism of nebivolol by the CYP 2D6 system, its dose should be reduced when it is coadministered with CYP 2D6 inhibitors. Nebivolol clearance may also be reduced in those patients with severe renal impairment and should be prescribed with caution in these patients. No studies have been conducted in dialysis patients.

Caution is warranted for patients with moderate hepatic impairment because of decreased metabolism. Patients with severe hepatic impairment have not been included in clinical trials, and nebivolol is contraindicated for this population.

Patients with bronchospastic disease should not receive beta blockers, including nebivolol. As with other beta blockers, nebivolol can mask the signs and symptoms of hypoglycemia and hyperthyroidism, specifically tachycardia.

It is not known whether nebivolol affects serum glucose levels; therefore, patients who are receiving treatment for diabetes should be informed about potential adverse effects. For patients with hyperthyroidism, the concern is greatest during abrupt discontinuation of beta-blocker therapy, which can potentiate hyperthyroid exacerbation or thyroid storm.

Exacerbation of angina, myocardial infarction, and ventricular arrhythmias may also occur as a result of abrupt discontinuation of nebivolol. When necessary, the nebivolol dose should be tapered slowly over one to two weeks. If angina worsens or if acute coronary insufficiency develops, nebivolol should be reinitiated immediately.

The use of nebivolol in compensated heart failure should also be used cautiously. If heart failure worsens, discontinuation of nebivolol therapy should be considered. Nebivolol has not been studied in angina or acute MI, and its use should thus be avoided at this time.

Caution should be exercised for those patients with peripheral vascular disease (PVD) and for patients who are taking non-dihydropyridine calcium-channel blockers. Beta blockers may exacerbate symptoms of arterial insufficiency in patients with PVD. For patients taking non-dihydropyridine calcium-channel blockers, such as diltiazem (Cardizem,

Table 1 Potential Drug Interactions with Nebivolol

Substrates of CYP 2D6		Inhibitors of CYP 2D6		Inducers of CYP 2D6
5-HT₃ receptors <ul style="list-style-type: none"> • Dolasetron • Ondansetron 	Cholinesterase inhibitors <ul style="list-style-type: none"> • Donepezil • Galantamine 	Antiarrhythmics <ul style="list-style-type: none"> • Amiodarone • Propafenone 	Pain agents <ul style="list-style-type: none"> • Celecoxib • Methadone • Propoxyphene 	Anti-seizure agents <ul style="list-style-type: none"> • Carbamazepine • Phenobarbital • Phenytoin
Antiarrhythmics <ul style="list-style-type: none"> • Encainide • Flecainide • Lidocaine • Mexiletine • Propafenone 	TCA's <ul style="list-style-type: none"> • Amitriptyline • Clomipramine • Desipramine • Imipramine • Maprotiline • Nortriptyline 	Antidepressants <ul style="list-style-type: none"> • Bupropion • Citalopram • Duloxetine • Escitalopram • Fluoxetine • Norfluoxetine • Paroxetine • Sertraline 	Protease inhibitors <ul style="list-style-type: none"> • Ritonavir • Tipranavir 	Others <ul style="list-style-type: none"> • Ethanol • Primidone • Rifampin
Antidepressants <ul style="list-style-type: none"> • Doxepin • Duloxetine • Fluoxetine • Fluvoxamine • Mirtazapine • Paroxetine • Trazodone • Venlafaxine 	Pain agents <ul style="list-style-type: none"> • Codeine • Fentanyl • Hydrocodone • Meperidine • Methadone • Morphine • Oxycodone • Propoxyphene • Tramadol 	Antihistamines <ul style="list-style-type: none"> • Chlorpheniramine • Diphenhydramine 	TCA's <ul style="list-style-type: none"> • Clomipramine • Desipramine 	
Antipsychotic agents <ul style="list-style-type: none"> • Chlorpromazine • Clozapine • Fluphenazine • Haloperidol • Olanzapine • Perphenazine • Quetiapine • Risperidone • Thioridazine 	Protease inhibitor <ul style="list-style-type: none"> • Ritonavir 	Antimalarial agents <ul style="list-style-type: none"> • Chloroquine • Halofantrine • Quinidine 	Others <ul style="list-style-type: none"> • Cinacalcet • Darifenacin • Imatinib • Moclobemide • Pomegranate • Propranolol • Quinacrine • Ranolazine • Terbinafine 	
Amphetamines <ul style="list-style-type: none"> • Amphetamine • Methamphetamine • Methoxyamphetamine 	Others <ul style="list-style-type: none"> • Atomoxetine • Cevimeline • Chlorpropamide • Cinacalcet • Cyclobenzaprine • Darifenacin • Dexfenfluramine • Dextromethorphan • Fenfluramine • Formoterol • Ranolazine • Tamoxifen • Tolterodine 	Antipsychotic agents <ul style="list-style-type: none"> • Fluphenazine • Haloperidol • Levomepromazine • Perphenazine • Thioridazine 		
Beta blockers <ul style="list-style-type: none"> • Bisoprolol • Carvedilol • Pindolol • Propranolol • Timolol 		DMARD <ul style="list-style-type: none"> • Hydroxychloroquine 		
		H₂ antagonists <ul style="list-style-type: none"> • Cimetidine • Ranitidine 		
		Illicit drugs <ul style="list-style-type: none"> • Cocaine 		

CYP = cytochrome; DMARD = disease-modifying antirheumatic drug; 5-HT₃ = 5-hydroxytryptamine (serotonin); TCA = tricyclic antidepressant. Based on data from *Pharm Lett* 2006;22(2):220-233.²²

Biovail) and verapamil (e.g., Calan, Pfizer), the negative inotropic and chronotropic effects may be additive. When these agents are used along with nebivolol, monitoring parameters must be applied for BP and electrocardiography.

Caution is also warranted in the perioperative state. If nebivolol is continued throughout anesthesia, patients should

be monitored for depressed myocardial function. The beta-blocking effects of nebivolol may be reversed by beta agonists such as dobutamine or isoproterenol (e.g., Isuprel, Abbott); however, this exposes the patient to an increased risk of severe hypotension and creates difficulty in regulating the heartbeat.

Nebivolol has been designated as a

Pregnancy C category medication because of its various effects noted in rats and pups. It is unknown whether this agent is excreted in human milk; however, because of the potential for beta blockers to produce serious adverse reactions in nursing infants (i.e., bradycardia), nebivolol is not recommended for use during nursing.

DOSAGE AND ADMINISTRATION¹³

The recommended starting dose of nebivolol is 5 mg once daily. The drug may be taken without regard to food. The dosage must be adjusted for each individual, according to the patient's BP. If additional reductions in BP are necessary, the dose may be increased slowly at two-week intervals up to a maximum dose of 40 mg daily.

In patients with renal insufficiency or moderate hepatic insufficiency, the recommended starting dose is reduced to 2.5 mg once daily. Nebivolol is not recommended for patients with severe hepatic impairment.

COST^{13,23}

Nebivolol is sold as 2.5-mg, 5-mg, and 10-mg unscored tablets in bottles of 30 and 100. The 5-mg and 10-mg tablets are also available in 10 × 10 unit-dose packages.

According to the 2008 edition of *Red Book*, the average wholesale price of a bottle of 30 tablets was \$54, a bottle of 100 tablets was \$180, and a 10 × 10 unit-dose package was \$180 regardless of strength.

CONCLUSION

Nebivolol is a cardioselective beta blocker approved for the treatment of hypertension. It produces unique nitric oxide-mediated vasodilatory effects, lacks intrinsic sympathomimetic activity, and possesses a tolerability profile similar to that of other beta blockers. Some studies suggest similar antihypertensive effects among patients using nebivolol, bisoprolol fumarate/HCT (Ziac, Duramed), atenolol (Tenormin, AstraZeneca), and metoprolol (Lopressor, Novartis);^{24–26} however, more data are needed to establish any advantages to selecting nebivolol over other agents.

Nebivolol has been available in Europe since 1999 to treat hypertension and heart failure. Several studies are currently under way to assess the efficacy and safety of nebivolol in patients with heart failure.²⁷

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